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Preterm birth: Inflammation, fetal injury and treatment strategies

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ABSTRACT

Preterm birth (PTB) is the leading cause of childhood mortality in children under 5 and accounts for approximately 11% of births worldwide. Premature babies are at risk of a number of health complications, notably cerebral palsy, but also respiratory and gastrointestinal disorders. Preterm deliveries can be medically indicated/elective procedures or they can occur spontaneously. Spontaneous PTB is commonly associated with intrauterine infection/inflammation. The presence of inflammatory mediators *in utero* has been associated with fetal injury, particularly affecting the fetal lungs and brain. This review will outline (i) the role of inflammation in term and PTB, (ii) the effect infection/inflammation has on fetal development and (iii) recent strategies to target PTB. Further research is urgently required to develop effective methods for the prevention and treatment of PTB and above all, to reduce fetal injury.

1. Introduction

The World Health Organisation defines preterm birth (PTB) as delivery before 37 completed weeks of gestation. PTB can be subdivided into extremely preterm (<28 weeks), very preterm (28–32 weeks) and moderate to late PTB (32–36 weeks) (WHO, 1977). In 2010, 14.9 million babies were born preterm, accounting for 11.1% of all births worldwide. Rates of PTB range from approximately 5% of births in European countries, to 18% in certain African countries (Blencowe et al., 2012). PTB is currently the leading cause of childhood mortality in children under 5 years (Harrison and Goldenberg, 2015). The economic burden of PTB to the public sector is estimated to be >£2.9 billion (Mangham et al., 2009). Much of the economic burden can be attributed to neonatal intensive care, often followed by ongoing health care and educational requirements, in addition to the emotional impact experienced by families (Howson et al., 2013).

PTB can be medically indicated/iatrogenic or spontaneous. Medically indicated PTB accounts for approximately a third of PTBs in high income countries (Rubens et al., 2014). This occurs when the risk to the fetus or mother outweighs the benefit of continuing the pregnancy, for instance in conditions such as preeclampsia and diabetes. Approximately 70% of PTBs are spontaneous, with women presenting with preterm labour (PTL) with cervical dilation or preterm premature rupture of membranes (Rubens et al., 2014).

PTL can be initiated by multiple mechanisms, including infection or inflammation, uteroplacental ischaemia or haemorrhage, uterine overdistension or stress (Goldenberg et al., 2008; Romero et al., 1994). Maternal risk factors include extremes in maternal age, body mass index (BMI), multiple gestation, the use of assisted reproductive technologies, history of PTB and low socioeconomic status (Rubens et al., 2014). Race is also an important risk factor, with women classified as black, African-American or Afro-Caribbean at greater risk of PTB than other ethnic groups (Goldenberg et al., 2008).

Due to the immaturity of multiple organ systems, premature newborns are at risk of a number of health complications (Rubens et al., 2014). As you would expect, the severity of complications inversely correlates with gestational age (WHO, 1977). Children born prematurely have an increased risk of cognitive and neurological impairment such as cerebral palsy, as well as respiratory and gastrointestinal complications (Goldenberg et al., 2008; Marlow et al., 2005). There is also the increased risk of chronic diseases in adulthood, such as obesity, diabetes and hypertension (Rubens et al., 2014). Interestingly, neonatal outcomes are sex-specific. Premature males are at greater risk of morbidity and mortality than females. In one premature cohort, the males had poorer neurological and respiratory outcomes, when followed up at 2 years of age (Peacock et al., 2012).

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2. Inflammation in labour and preterm labour

Human parturition is an inflammatory process (Bollapragada et al., 2009). Labour is initiated by the shift from a quiescent to a pro-inflammatory environment, instigating a three step process, characterised by uterine contractility, cervical ripening and membrane activation/rupture (Rinaldi et al., 2011; Romero et al., 1994). Cytokines are essential in the initiation and regulation of this process (Bowen et al., 2002).

Monocytes and neutrophils are primed in the peripheral blood in association with both term and PTL (Yuan et al., 2009). These cells infiltrate the human myometrium and cervix during spontaneous term labour, which is associated with a significant increase in interleukin (*IL*)-*1β, IL-6* and *IL-8* gene expression (Bokstrom et al., 1997; Osman et al., 2003; Thomson et al., 1999). Stromal cells of the maternal and fetal tissues are also responsible for the release of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8 and tumour necrosis factor alpha (TNFα) (Young et al., 2002). Myometrial contractions are stimulated by the increase of IL-1β and TNFα, which increase calcium entry into these myometrial smooth muscle cells (Barata et al., 2004; Tribe et al., 2003). Prostaglandins, $PGF_{2\alpha}$ and PGE_2 are also involved in the stimulation of myometrial contractions (Olson, 2003). Cervical ripening is an inflammatory event in both term and PTB (Osman et al., 2003; Tornblom et al., 2005). Pro-inflammatory cytokines stimulate matrix metalloproteinase (MMP) expression, such as MMP-9, which promotes extracellular matrix degradation and cervical remodelling (Larsen and Hwang, 2011).

There is also a significant increase in leukocyte recruitment to the fetal membranes during parturition, with an increase in IL-1β, IL-8, and TNFα (Gomez-Lopez et al., 2009). Normal and preterm rupture of membranes differ in regional chemotactic activity and related chemokine/cytokine production, which may suggest differential mechanisms of rupture (Gomez-Lopez et al., 2013). The choriodecidua is responsible for granulocyte, T-cell lymphocyte, monocyte and NK cells chemoattraction (Gomez-Lopez et al., 2011). Leukocytes infiltrate the decidua during labour at term and in PTL and play a role in stimulating inflammatory mediators involved in decidual activation (Hamilton et al., 2012; Osman et al., 2003). Macrophage numbers are increased in term and PTL but neutrophil abundance is only significantly increased in the decidua in PTL with infection (Hamilton et al., 2012).

Nuclear factor-κB (NF-κB) is a pleiotropic transcription factor which is commonly associated with inflammation, as it is activated by and regulates pro-inflammatory cytokines. NF-κB activity is central to labour-associated pathways. It is required for both prostaglandin synthesis and for the regulation of MMP expression and thus, important for the stimulation of uterine contractions and cervical ripening. The premature or pathological activation of NF-κB could subsequently contribute to the initiation of PTL (Lindstrom and Bennett, 2005).

3. Fetal injury

Intrauterine infection/inflammation is a common cause of PTL. Presence of such an adverse *in utero* environment can lead to fetal injury. Chorioamnionitis, characterised by inflammation of the fetal membranes as a result of bacterial infection, is a risk factor for conditions such as cerebral palsy, necrotising enterocolitis and patent ductus arteriosus (Been et al., 2013; Park et al., 2015; Wu and Colford, 2000). Bacteria or inflammatory mediators may reach the fetal circulation by placental transmission into the umbilical cord or indirectly via the amniotic fluid, resulting in fetal injury (Adams Waldorf and Mcadams, 2013) (Fig. 1).

Intra-amniotic inflammation is also associated with lung injury. Elevated levels of inflammatory mediators such as TNF-α, IL-1β, IL-6 and IL-8 in the amniotic fluid have been found in women who had babies with bronchopulmonary dysplasia (BPD), a chronic lung disease affecting infants (Ambalavanan et al., 2011; Yoon et al., 1997b). However, a meta-analysis found only a modest association between chorioamnionitis and BPD (Hartling et al., 2012). Intra-amniotic endotoxin administration in a sheep model led to fetal lung injury, identified by evidence of inflammation, cell death and remodelling (Kramer et al., 2002). Exposure to endotoxin *in utero* also affects the development of the fetal ovine lung. One study observed an increase in alveolar volume, while the total number of alveolar was significantly reduced. Thinning of the alveolar walls was also observed (Willet et al., 2000). In a chronically catheterised sheep model of the extreme preterm period, lipopolysaccharide (LPS) exposure caused fetal skin and lung inflammation, as well as systemic inflammation (Kemp, 2014; Kemp et al., 2016). The premature fetus rapidly generated a robust inflammatory response to intra-amniotic LPS, which was driven by amniotic fluid-exposed tissues. Fetal blood cells responded to systemic inflammation but didn't contribute to the acute production of inflammatory mediators (Kemp et al., 2016). Furthermore, a primate model of transient choriodecidual infection confirmed indirect lung injury as result of elevated inflammatory mediators. This led to the downregulation of pathways for angiogenesis, morphogenesis and cellular growth and development in the fetal lung (Mcadams et al., 2012). In addition to conditions such as neonatal BPD, the treatment premature babies receive can have an adverse effect on pulmonary development and lead to long term, altered lung function. A follow up study reported evidence of airway obstruction from mid-childhood to adulthood in a preterm-born cohort (Vollsaeter et al., 2013).

Prematurity has also been associated with an increased incidence of brain damage. This can result in neurological conditions such as cerebral palsy, which is often observed in conjunction with intraventricular haemorrhage or periventricular leukomalacia (Chang, 2015). Additionally, inflammation during fetal and neonatal development has been linked to other neuropathologies such as schizophrenia and autism. It has been suggested that schizophrenia may be as a result of post-acute latent inflammation, whereas autism may be due to persistent inflammation (Meyer et al., 2011).

The release of pro-inflammatory mediators can play a role in the generation of brain white matter lesions. Evidence of elevated levels of IL-1β and IL-6 in the amniotic fluid has been used to identify premature newborns at risk of developing these lesions (Yoon et al., 1997a). TNFα signalling, in particular, has been described as toxic to developing oligodendrocytes (Li et al., 2008). The isolation of low-virulence microorganisms from preterm placentas, such as common skin microflora, has been associated with brain lesions and cerebral palsy in these infants. Evidence of placental inflammation alone, is a predictor of brain injury (Leviton et al., 2010). Even in the absence of PTB, fetal brain injury was reported in a mouse model of intrauterine inflammation (Elovitz et al., 2011). The same group reported damage to fetal neurons, demonstrated by a significant reduction in microtubule-associated protein 2 (*Map2*) gene expression, as well as altered neuronal morphology and neurotoxicity, in this model (Burd et al., 2011). Dada et al. (2014) found that following intrauterine inflammation, brain injury is not only acute. Long term changes in MRI and behaviour are observed even in adulthood. Chronic brain inflammation was linked to eventual neuronal loss. In addition, these effects were found to be sex specific, with male mice more susceptible to long-term neurologic injury. Mallard et al. (2003) exposed fetal sheep to LPS during mid-gestation and reported microglia activation, astrocyte damage and oligodendrocyte death. Inflammation may cause brain injury as a result of direct insult to oligodendrocytes and neurons or as secondary injury via microglial cell activation. This subsequently results in the secretion

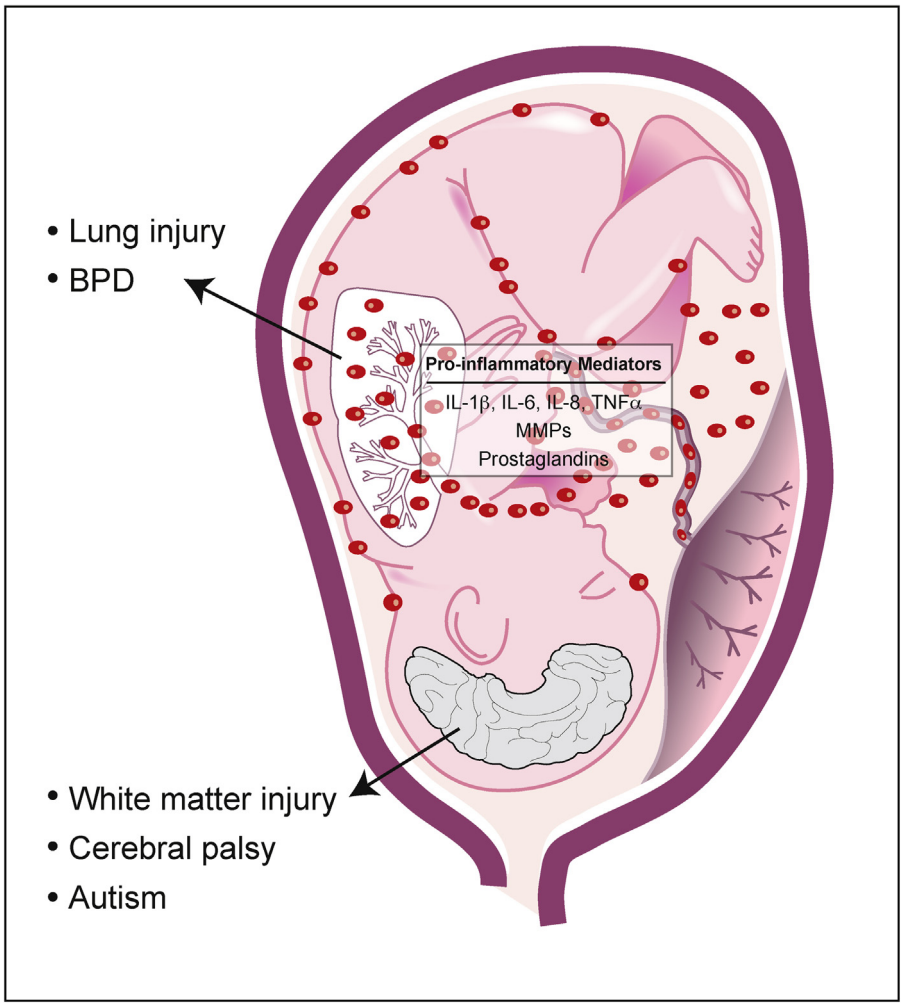

Fig. 1. Intrauterine inflammation and fetal injury.
Human parturition is an inflammatory process. However, the presence of inflammation earlier in gestation can result in the preterm, pathological initiation of labour, with adverse consequences for the fetus. Inflammatory mediators may reach the fetal circulation by placental transmission into the umbilical cord or indirectly via the amniotic fluid. Amniotic fluid exposed tissues, such as the fetal skin and lung, can drive the fetal inflammatory response. Prolonged *in utero* exposure to inflammatory mediators can result in fetal injury. The fetus is susceptible to lung injury and bronchopulmonary dysplasia (BPD), as well as brain white matter lesions and neurological conditions such as cerebral palsy and autism.

of pro-inflammatory cytokines, causing damage to surrounding cells (Burd et al., 2012).

4. Prevention and treatment of PTL

In general, tocolytic therapies are largely ineffective at substantially delaying delivery and reducing neonatal mortality (Haas et al., 2012). Several trials have reported the benefits of vaginal progesterone administration for reducing the rates of PTB and improving neonatal outcome. However, these studies had limited information on the long term outcome of these infants (Da Fonseca et al., 2003; Dodd et al., 2013; Fonseca et al., 2007; Hassan et al., 2011). Recently, a large, double-blind, randomised, placebo controlled trial of vaginal progesterone treatment reported that the risk of PTB was not reduced by progesterone nor was neonatal outcome improved, in women who were at risk of PTB. The trial did not find any long term benefit of this treatment in children by the time they were 2 years of age (Norman et al., 2016).

As intrauterine infection is a common cause of PTL, antibiotics have previously been considered a logical method of treatment. However, the use of antibiotics to prevent PTB has been associated with neonatal enterocolitis, as well as an increased risk of cerebral palsy (Kenyon et al., 2001; Kenyon et al., 2008). As parturition is associated with leukocyte influx into the intrauterine tissues, immunomodulation has been investigated in mouse models of PTB, using leukocyte depletion. Rinaldi et al. (2014) found that neutrophil depletion did not delay delivery in an LPS-mediated PTB mouse model, despite having an important role in the inflammatory response in the intrauterine tissues. Filipovich et al. (2015) further corroborated this finding by reporting that polymorphonuclear leukocyte depletion in an *E. coli* model of PTB did not prevent premature birth. Therefore, neutrophil infiltration is not essential for the induction of murine infection-induced PTB. However, macrophage depletion was found to successfully prevent both RU486 and LPS-induced PTB in mice (Gonzalez et al., 2011).

Targeting the inflammation commonly associated with PTB may be a suitable approach to delay the onset of parturition and prevent fetal injury. A recent review outlined the possible targets for such treatments including non-specific NF-kB inhibitors, toll-like receptor 4 (TLR4) antagonists, TNFα biologics and novel cytokine suppressive anti-inflammatory drugs (CSAIDs) (Ng et al., 2015; Stinson et al., 2014). Shynlova et al. (2014) targeted the activiation of murine peripheral maternal immune cells with a broad spectrum chemokine inhibitor. A reduced incidence of LPS-induced PTB

was reported, in additon to reducing both immune cell infiltration into maternal tissues and inflammatory mediator secretion. Other novel, naturally produced or alternative therapies such as folic acid, melatonin and statins, have recently been investigated for the treatment of PTB and fetal loss in mouse models (Boyle et al., 2015; Dominguez Rubio et al., 2014; Gonzalez et al., 2014; Zhao et al., 2013). Antigen capture therapy has been described in an ovine model of intrauterine infection/inflammation. This cationic peptide antibiotic, polymyxin B, binds to *E. coli*, reducing inflammation in the amniotic fluid and fetal lung (Saito et al., 2014). Rinaldi et al. (2015) investigated the use of a key anti-inflammatory and pro-resolution mediator, 15-*epi*-lipoxin A_4, in an LPS-induced PTB mouse model. Although PTB was not prevented, 15-*epi*-lipoxin A_4 reduced rates of fetal death.

It is unlikely that one treatment will be successful in preventing the multifactorial syndrome of PTB. However, it should be considered that combination therapies, which have both tocolytic and fetal protective effects, would be advantagous. Improved methods of identifying at risk mothers and fetuses are also required to effectively target treatments and avoid unnecessary harm. Using new ultrasound techniques, such as Tissue Doppler Imaging (TDI), to identify signs of fetal inflammation is one strategy that shows promise (Di Naro et al., 2010; Stock et al., 2016). The influence genotype may have on the therapeutics used for PTB prevention and treatment, has recently been discussed. Although the evidence to date is limited, there is increasing indication that pharmacogenomics may play a role in PTB. By integrating clinical information, environmental influences and genotype, a more comprehensive strategy to personalised medicine could be optimised (Manuck, 2016).

5. Conclusion

PTB is still a significant public health problem. This syndrome is multifactorial and its etiology is not well understood. Inflammation is necessary to stimulate term labour. However, its presence earlier in pregnancy contributes to fetal injury, particularly to the lung and brain. Evidence of inflammatory mediators in the amniotic fluid identifies infants at risk of lung damage and brain white matter lesions. Delaying PTB, as well as improving the outcome of the babies, has proved a great challenge. Current therapies, such as vaginal progesterone treatment, are ineffective. In addition, the use of antibiotics to target intrauterine infection is potentially harmful to the developing fetus, increasing the risk of cerebral palsy. Animal models are currently being utilised to investigate potential therapeutic agents which may target the intrauterine inflammation with the intention of protecting against fetal injury. The possibility of developing more personalised medicine should also be considered in the effort to reduce the rates of fetal mortality and morbidity, as a result of this clinical condition.

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